Hemoglobinopathies (Sickle Cell Disease and Thalassemia)

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Barbara Cappelli, Eliane Gluckman,
Khaled Ghanem, and Miguel R. Abboud

79.1 HSCT for Sickle Cell Disease

Barbara Cappelli and Eliane Gluckman

79.1.1 Definition and Epidemiology

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy worldwide. It results from a single-nucleotide substitution that leads to a propensity toward hemoglobin polymerization and sickling of red blood cells. Sickle cell disease is characterized by anemia, ongoing hemolysis, and acute and chronic vaso-occlusive complications affecting multiple organs. SCD affects over 100,000 Americans, and it occurs in about one in 500 African-American births and in one in every 1000–1400 Hispanic-American births (NIH 2014; Piel et al. 2013).

The implementation of newborn screening, penicillin prophylaxis, vaccination programs, narcotics, chronic transfusions, hydroxyurea, and the early detection of cerebral vasculopathy with transcranial Doppler (TCD) have improved the perspective for children with SCD (Angelucci et al. 2014; Yawn et al. 2014; Ware et al. 2016; Bernaudin et al. 2016).

B. Cappelli
Eurocord-Monacord, Centre Scientifique de Monaco, Monaco, Monaco

E. Gluckman (✉)
Eurocord, Department of Hematology, Hospital Saint Louis, University Paris-Diderot, Paris, France
e-mail: eliane.gluckman@aphp.fr

K. Ghanem
BASMA Pediatric Oncology Unit,
Al Bairouni Hospital, Damascus, Syria

M. R.Abboud
Department of Pediatrics and Adolescent Medicine,
American University of Beirut Medical Center,
Beirut, Lebanon

79.1.2 Allo-HSCT with an HLA Identical Sibling

HSCT remains the only curative therapy for SCD (Angelucci et al. 2014; Arnold et al. 2016; Gluckman et al. 2017). The goal when performing HSCT is to replace the patient's marrow with genetic functional cells before major organ dysfunction and complications (Bernaudin et al. 2007). Some of the most common indications for HSCT are listed in Table 79.1 (Angelucci et al. 2014; Bernaudin et al. 2016).

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Several barriers prevent HSCT widespread application including lack of a suitable donor, lack of information, and limited understanding of HSCT. Moreover, HSCT encompasses a risk of early- and late-onset regimen-related toxicities, rejection, and mortality. Nevertheless, the annual number of transplants have been increasing and has quadrupled in the last decade (CIBMTR personal communication). The first successful HLA identical HSCT was performed in a patient affected by both SCD and AML in 1984 (Johnson et al. 1984). After that, many groups have described a series of patients transplanted from an HLA identical sibling with an OS that varies between 91 and 100% and EFS that varies between 73 and 100% (Bernaudin et al. 2007; Walters et al. 2016). Recently, 1000 HLA identical transplants, performed between 1986 and 2013 and reported to EBMT, Eurocord, and the CIBMTR, have been published with a 5-year EFS and OS of 91.4% (95% CI 89.6–93.3%) and 92.9% (95% CI 91.1–94.6%), respectively. The EFS and OS were both lower with increasing age, EFS was higher for transplantations performed after 2006, and OS was lower for peripheral blood transplant recipients (Fig. 79.1) (Gluckman et al. 2017).

Table 79.1 Indications for HSCT in SCD patients

Age <16 years	
HLA identical sibling donor	
One or more of the following complications:	Stroke or central nervous system event lasting >24 h
	Sickle lung disease
	Sickle nephropathy
	Retinopathy
	Osteonecrosis
	Red-cell alloimmunization
	Acute chest syndrome
	Recurrent priapism
	Recurrent vaso-occlusive painful episodes
	Failure to benefit or unable or unwilling to continue supportive care therapy including hydroxyurea
	Impaired neuropsychological function with abnormal cerebral MRI and angiography
	Abnormal transcranial Doppler velocities

Modified from (Angelucci et al. 2014)

79.1.3 Indications

Indication for HSCT for "less severe patients" before significant organ damage has occurred is open to discussion. In fact, on one hand, it would be better to transplant them early in order to pre-

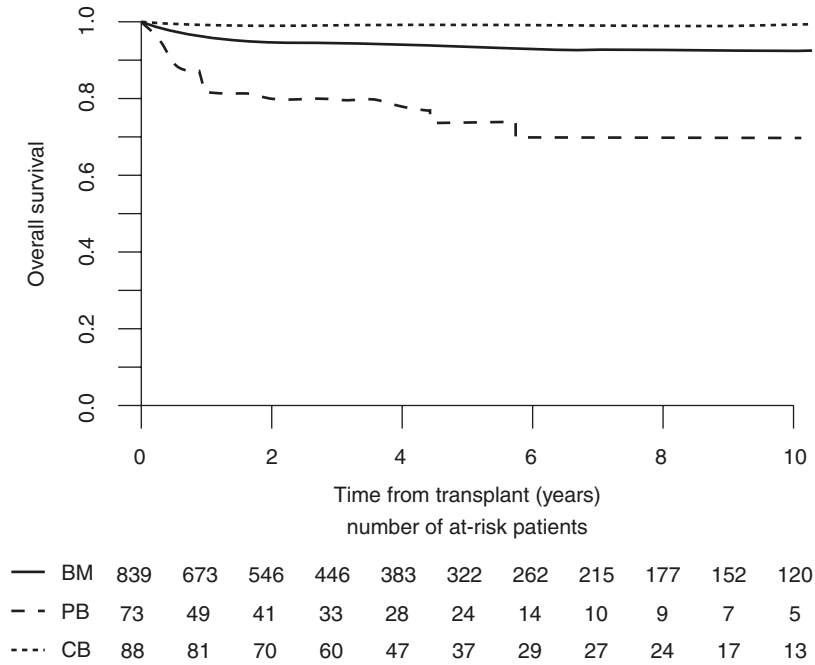

Fig. 79.1 Overall survival according to stem cell source on 1000 SCD patients transplanted from an HLA identical sibling (Gluckman et al. 2017)

vent early organ damage secondary to SCD, avoid SCD complications in childhood, and achieve better HSCT outcomes secondary to less pre-HSCT organ damage and alloimmunization and, on the other hand, it could be considered to wait to perform an HSCT for the establishment of new available SCD supportive cares (new medications other than hydroxyurea), promising curative therapies (gene therapy), and advances in HSCT technology, others may be available. Nevertheless, it has been demonstrated that patients transplanted at a young age have a better 3-year OS and 3-year EFS, with lower incidence of aGvHD and cGvHD (Gluckman et al. 2017). These findings outline the importance of early referral to HSCT for SCD patients.

79.1.4 Conditioning

To date, a myeloablative conditioning regimen (especially with BU/CY + ATG) is the gold standard for HLA identical sibling HSCTs (EFS: 73–96%, OS: 91–100%) despite the risk of long-term transplant-related toxicity (Bernaudin et al. 2007; Walters et al. 2016). A conditioning regimen including FLU and BU has been used but with high GvHD risk; therefore, it should be considered to add ATG to the conditioning regimen to lower the GvHD risk in these patients.

A RIC regimen has been explored to decrease toxicity and allow a stable, mixed chimerism. The aim of a tailored conditioning regimen in children is to preserve fertility, whereas in adults is to reduce toxicity in severely compromised patients due to their underlying disease. Several reduced intensity conditioning regimens (FLU/MEL + ALEM +/− TT or ALEM + TBI 300 cGy +/− PT-CY or FLU/CY or TBI 300 cGy +/− ATG) have been used in many small patient series but with high degree of graft rejection (Talano and Cairo 2015; Arnold et al. 2016). Thus, recently, encouraging outcomes and low early- and long-term toxicity have been confirmed by other groups after FLU-based RIC regimens (Bhatia et al. 2014). Lately, 13 high-risk patients conditioned with a chemotherapy-free regimen (ALEM-TBI 300 cGy) have shown a 92% DFS and 100% OS (Saraf et al. 2016).

Moreover, a prospective multicenter trial comparing allogeneic matched related HSCT after a RIC regimen, with standard of care in adolescents and adults with severe SCD, has shown encouraging preliminary results (Dhedin et al. 2016).

Despite MAC dosing in the conditioning regimens, a mixture of both donor and recipient hematopoietic cells (mixed donor chimerism) can be consistently observed in approximately 10–20% of these children (Bernaudin et al. 2007; Walters et al. 2016). Interestingly, this mixed chimeric state with the presence of both recipient and donor blood cells is sufficient to direct bone marrow to preferentially produce donor-type hemoglobin (rather than abnormal hemoglobin of the recipient), and red cells revert the SCD phenotype, and minimize the risk of GVHD, confirming the therapeutic efficacy of mixed chimerism for hemoglobinopathies. New studies on mixed chimerism are ongoing.

79.1.5 Alternative Donors

Finding a potential MUD is based on the ethnic and racial background; for SCD patients the probability for an 8/8 HLA MUD or CB donor is less than 18%. Nevertheless, some small series of patients using URD have been published, but for now relapse rate and GvHD risk remain unacceptable (Justus et al. 2015).

Strategies that explore the use of mismatched related (haplo) donors are ongoing (Dallas et al. 2013; Talano and Cairo 2015). Recently promising results of CD3+/CD19+ depleted T-cell haplo-HSCT after TREO/FLU/TT + ATG have been shown to be safe and efficient with a low incidence of GvHD in advanced stage SCD (Foell et al. 2017).

Moreover, new strategies using gene therapy have been recently published with encouraging results (Ribeil et al. 2017), and the use of gene editing is being explored for this single-mutation disease (Canver and Orkin 2016).

79.2 Thalassemia

Khaled Ghanem and Miguel R. Abboud

79.2.1 Introduction

The outcome of thalassemia major (TM, transfusion-dependent thalassemia) has improved dramatically over the past two decades due to improvements in supportive care and iron chelation therapy (Taher et al. 2018). Life expectancy for TM patients exceeds 40 years, and it is no longer significantly different from the life expectancy of thalassemia intermedia patients, in developed countries (Vitrano et al. 2017).

Match family donor (MFD) allo-HSCT is currently considered the only curative standard therapeutic approach for TM, which despite holding its own risks, could release the patient from lifelong treatments, and possible iron accumulation complications. Despite encouraging results of gene therapy, its use is currently limited to clinical trials.

79.2.2 Best Transplant Candidates

In late 1990s, the Pesaro group has proposed a risk classification for pediatric patients undergoing MFD HSCT for TM (Lucarelli et al. 1998). The classification depended on three risk factors (Table 79.2) and was validated in the pediatric population; however, it did not predict risk in adult patients (Angelucci et al. 2017). Limitations to this risk stratification include the interobserver variability regarding hepatomegaly and the lack of clear definition of adequate iron chelation. The Pesaro classification is applicable in the setting of best medical care. In developing countries, where medical care might not be optimal, a very-high-risk group was identified in Pesaro class 3 patients if liver size is >5 cm below the costal margin and if the patient age is >7 years (Mathews et al. 2007). The EBMT has recently identified the age of 14 years as the oldest age for optimal outcome in MFD HSCT for TM (Baronciani et al. 2016).

Accurate assessment of iron content in the liver and heart is crucial before proceeding to transplant. No consensus is currently available regarding the best method of iron content assessment in both organs. Serum ferritin level might not reflect accurately the severity of iron overload. Liver biopsy is the gold standard; however, it carries the risks of the invasive procedure. Transient elastography (FibroScan) and T2 MRI have been shown to be reliable noninvasive methods to predict liver fibrosis secondary to iron overload, for TM patients who are candidates to HSCT (Hamidieh et al. 2014; Hamidieh et al. 2015).

Table 79.2 Pesaro classifications for risk assessment prior to HSCT for TM (Lucarelli et al. 1998)

Risk factor	Class 1	Class 2 (min. 1, max. 2)	Class 3
Inadequate chelation	×	×/✓	✓
Hepatomegaly >2 cm	×	×/✓	✓
Portal fibrosis	×	×/✓	✓

79.2.3 Conditioning Regimens

The use of the myeloablative BU and CY as the conditioning regimen for HSCT for TM has been the standard practice, due to the increased marrow activity and the allo-sensitization in heavily transfused patients (Lucarelli et al. 1990). However, this regimen was associated with hepatic and cardiac toxicity due to the iron overload and the toxic hepatic and cardiac effects of BU and CY, respectively.

ATG or ALEM have been added in some protocols to the conditioning regimen to prevent GvHD and enhance engraftment (Law et al. 2012; Mohty 2012). Despite being effective with low incidence of infections, the use of these agents is still debatable.

In an attempt to reduce the extramedullary toxicity of BU and CY, a non-myeloablative regimen of TREO/FLU/TT has been used with encouraging results (Bernardo et al. 2012). Defibrotide has been used successfully to prevent SOS/VOD in patients with TM undergoing

HSCT with conditioning regimen containing IV BU (Cappelli et al. 2009). The use of BU pharmacokinetics was associated with better engraftment and less toxicity (Gaziev et al. 2010); however, these studies are available in limited number of institutions worldwide.

79.2.4 Alternative Donors

79.2.4.1 Matched Unrelated Donors (MUD)

In case MFD is not available, the discovery of high-resolution HLA typing techniques made the performance of successful MUD transplant possible. The probability of finding a matched unrelated donor varies between 50% in Caucasians to less than 10% in some minorities (Rocha and Locatelli 2008). With the use of BU, CY, TT, and FLU as conditioning regimen and ATG, MMF, and short-course MTX as GvHD prophylaxis, the outcome of PBSC MUD in TM was comparable to MFD HSCT in regard to OS, TRM, TFS, and aGvHD (Li et al. 2012).

79.2.4.2 Unrelated Umbilical Cord

The use of unrelated umbilical cord as a source of stem cells for HSCT in TM is hampered by the high incidence of graft failure due to the low stem cell dose. The graft failure rate could be as high as 57% (Ruggeri et al. 2011). This could be partially overcome by the use of double UCB units. The 5-year overall and thalassemia-free survival rates were 88.3 and 73.9%, respectively, when using two units instead of one if no single units included more than 25×10^6 total nucleated cells/kg of recipient weight. Other strategies to overcome the main barrier of low cell dose include co-transplantation of third-party mesenchymal stromal or TCD haploidentical cells (Kwon et al. 2014; Kim et al. 2004).

79.2.4.3 Haploidentical HSCT

Due to the low probability of finding a MUD in some ethnicities and the previously mentioned issues with umbilical-cord transplant, new strategies have been evolved to develop an effective and safe haploidentical transplant procedure for TM patients. The use of TCD graft was associated with high rate of infections and increased risk of graft failure due to allo-sensitization and hyperactive marrow (Gaziev et al. 2000). This was overcome by pretransplant over-transfusion and immunosuppressive therapy and post transplant infusion of transduced donor T-cells with gene-inducible caspase-9 (Bertaina et al. 2017). The use of T-cell replete grafts is still under investigation to explore the best strategy to prevent GvHD.

79.2.5 Mixed Chimerism

The incidence of mixed chimerism after HSCT for TM was reported to be around 12%. the risk of graft rejection in patients with mixed chimerism was high only if mixed chimerism had been observed within two months post-transplant. Most cases with late persistent mixed chimerism evolved into either stable chimerism or complete engraftment and did not require additional PRBC transfusion support (Andreani et al. 2000).

79.2.6 Post transplant Iron Chelation

Iron overload remains a problem after HSCT, and most investigators rely on phlebotomy to decrease excessive iron stores. In a recent phase II, multicenter, single-arm trial, deferasirox at a dose of 20 mg/kg/day, starting after a minimum of 6 months of transplant, and continued for 1 year, was safe and associated with decreased burden of iron overload after transplant (serum ferritin, liver, and cardiac iron content by MRI) (Yesilipek et al. 2018).

Key Points

- HLA identical sibling HSCT is an established treatment option for SCD.
- HSCT should be performed as early as possible, preferably at pre-school age, and BU, CY, and ATG should be used as conditioning regimen.
- Match family donor allo-HSCT is currently considered the only curative standard therapeutic approach for thalassemia major, which despite holding its own risks, could release the patient from lifelong treatments and possible iron accumulation complications.
- Despite encouraging results of gene therapy, its use in TM is currently limited to clinical trials.

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